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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,008	05/06/2002	Steven K Libutti	14014.0322U2	3848

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NATIONAL INSTITUTE OF HEALTH
C/O NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30303

EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
06/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/031,008	Applicant(s) LIBUTTI ET AL.	
	Examiner Michael D. Burkhart	Art Unit 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *14 May 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2, 4, 16, 18, 21, 22 and 40*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Joe Waitel
AU1633

Continuation of 5. Applicant's reply has overcome the following rejection(s): 35 USC 102(b) rejection of claims 1, 2, 4, 18, 21, and 22; 35 USC 112 2nd rejection of claim 40.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al in view of Restifo et al. This rejection is maintained for reasons made of record in the Office Actions dated 2/22/2006, 11/9/2006, and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 5/14/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) there is no motivation to combine the Restifo et al and Li et al references because of a difference in size and structure of the respective proteins taught by the references; 2) Restifo et al does not present a reasonable expectation for success for the generic suggestion that the E19 signal sequence could direct secretion of a protein of from 5 to 1000 amino acids; 3) Restifo et al does not present a reasonable expectation for success for the expression of an antiangiogenic protein resulting in increased circulating levels and antiangiogenic acitivity; 4) Restifo et al is not a scientific publication, and there is no scientific validity or basis for the expression/secretion of any other protein than the E19/9-mer peptide taught by Restifo et al; 5) the fact that the E19 signal sequence naturally directs the secretion of a 19 kD adenoviral protein does not suggest it could direct secretion of a heterologous protein, such as an antiangiogenic protein at levels sufficient to achieve antiangiogenic activity; 6) Li et al does not teach the use of an adenoviral signal sequence to direct secretion of angiostatin, and other than the plasminogen secretion signal does not teach the use of any other signal sequence to drive secretion of angiostatin, thus it cannot be assumed that substituting another signal sequence to drive angiostatin secretion would be efficacious; 7) the plasminogen signal sequence naturally directs secretion of plasminogen, of which angiostatin is a fragment, thus, one of skill in the art would understand from the teachings of Li et al and Griscelli et al that in order to secrete an anitangiogenic protein, a signal sequence "naturally" associated with the antiangiogenic protein would have to be used; 8) there is no reasonable expectation that linking an adenoviral signal sequence to an antiangiogenic protein would lead to the claimed properties of increased circulating levels of an antiangiogenic protein or the ability to treat tumors by systemic delivery.

Regarding 1) - 8) above, again, applicants present no evidence, only assertion and supposition, in the arguments against the instant rejection. "Argument of counsel cannot take the place of evidence lacking in the record." In re Scarborough, 182 USPQ 298, 302 (CCPA 1974). Furthermore, regarding 1) - 8) above, applicants present a limited description of the cited references and ignore facts presented in previous Office Actions and taught by the references, primarily that the use of a plasminogen signal sequence is the only signal sequence used in Li et al, and that angiostatin is naturally associated with the plasminogen signal sequence.

Regarding 1), both references involve the gene therapy of cancer by recombinant viruses. Ample motivation and suggestion to combine the references was presented in the Office Action dated 2/22/2006, primarily, that the skilled artisan would by motivated to treat cancer with the compositions taught in Restifo et al and Li et al.

Regarding 2) and 4), Restifo et al indicate the signal sequence may precede another peptide from 5 to 1000 amino acid resides (column 4, lines 32-40). Prior art is presumed to be enabling, absent evidence to the contrary, not unsupported assertions, see MPEP 2121. Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al would be unexpected.

Regarding 2) - 4), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding 3), 5) and 8), in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increased circulating levels of an antiangiogenic protein and antiangiogenic acitivity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding 5), the E19 signal sequence directed expression and secretion of a heterologous protein for reasons made of record, i.e. the teachings of Restifo et al.

Regarding 6), these statements are incorrect. For reasons of record, Li et al clearly teaches signal sequences (uPA and plasminogen, at the least, general signal sequences are disclosed in column 9, lines 44-53) to direct the secretion of antiangiogenic proteins (fragments of urokinase, angiostatin and endostatin, at the least) expressed from the adenoviral vectors (see the Examples). Thus, in contrast to applicants unsupported assertions, the prior art teaches that heterologous signal sequences can direct the expression of antiangiogenic proteins (and literally any other protein, for that matter). Furthermore, the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of the protein and prevented tumor establishment and growth (Griscelli et al 1998, PNAS, see in particular page 6371, first column, first full para.).

Regarding 7), the plasminogen signal sequence is not naturally associated with angiostatin, which is an internal fragment of plasminogen (amino acids 98-440) generated by hydrolysis of plasminogen by a protease (Griscelli et al, page 6367, second column). Thus, the secretion of angiostatin by the plasminogen signal sequence is considered the secretion of a heterologous protein, as the plasminogen signal sequence is not "naturally" associated with the angiostatin fragment. This is why the prior art teaches fusion proteins of a signal sequence linked to angiostatin. Furthermore, a reading of the references reveals no teachings that a secretion signal must be "naturally" associated with the protein to be excreted. Rather, it is indicated that any signal sequence, in general, may be used. See column 9, lines 44-53 of Li et al.